Claims

1. A chemical compound or composition comprising a peptide, which peptide comprises a β-strand-forming section of peptide which forms a β-strand having two edges, a first edge which associates with a target β-strand formed by a separate peptide-containing molecule, and a second edge, wherein the β-strand-forming section of peptide comprises a sequence of at least four consecutive α-L-amino-acid residues, all of which sterically permit the β-strand-forming section of peptide to form a β-strand, have side chains able to form strong non-covalent interactions with neighbouring side chains of the target β-strand, and at least one of which is an Nα-substituted α-L-amino-acid residue, and any two successive Nα-substituted α-L-amino-acid residues are separated by an odd number of consecutive Nα-unsubstituted α-L-amino-acid residues, such that the Nα-substituent(s) lie along only the said second edge.

2. A chemical compound or composition according to claim 1, wherein no two successive Nα-substituted amino-acid residues in the β-strand-forming section of peptide are separated by more than 3 consecutive Nα-unsubstituted amino-acid residues.

3. A chemical compound or composition according to claim 1 or claim 2 wherein successive Nα-substituted α-L-amino-acid residues in the β-strand-forming section of peptide are separated from each other by single Nα-unsubstituted α-L-amino-acid residues, such that the β-strand-forming section of peptide comprises an alternating sequence of Nα-substituted and Nα-unsubstituted α-L-amino-acid residues.

4. A chemical compound or composition according to any preceding claim wherein the Nα-substituent of each Nα-

substituted α-L-amino-acid residue in the β-strand-forming section of peptide sterically allows or promotes the β-strand-forming section of peptide to form a β-strand, and sterically hinders the association of the said second edge of that β-strand with another β-strand.

5. A chemical compound or composition according to claim 4, wherein the Nα-substituent of each Nα-substituted α-L-amino-acid residue in the β-strand-forming section of peptide sterically hinders the action of proteolytic enzymes on the β-strand-forming section of peptide.

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6. A chemical compound or composition according to claim 4 or claim 5, wherein the Nα-substituent of each Nα-substituted α-L-amino-acid residue in the β-strand-forming section of peptide is selected from the group consisting of:

a fluorine atom or an OH group;

a group that is connected to the Nα atom by an oxygen atom within it;

a group that is connected to the Nα atom by a CH_2 subgroup within it;

a methyl or ethyl group, or some other alkyl or aliphatic group;

a substituted or unsubstituted benzyl group, or some other arylmethyl group;

an acetylated or acylated 2-hydroxy-4-methoxybenzyl (AcHmb) group; and

an acylated or unacylated 2-hydroxybenzyl (AcHb/Hb) group.

7. A chemical compound or composition according to any preceding claim, wherein the side chain of each α-L-amino-acid residue in the β-strand-forming section of peptide allows or promotes the β-strand forming section of peptide to form a β-strand .

8. A chemical compound or composition according to claim 7, wherein the side chain of one or more α-L-amino-acid residues in the β-strand forming section of peptide is that of an amino-acid residue having a β-sheet propensity of greater than 1.00.

9. A chemical compound or composition according to claim 7, wherein the side chain of one or more α-L-amino-acid residues in the β-strand forming section of peptide is selected from the group consisting of:

an atom or group that allows or promotes the β-strand-forming section of peptide to associate as a β-strand with the target β-strand and thereby form a stable β-sheet complex; and

an atom or group that forms a hydrophobic or electrostatic interaction, hydrogen bond, or other favourable non-covalent interaction with the neighbouring side chain of the target β-strand in a β-sheet complex comprising the target β-strand and the β-strand forming section of peptide.

10. A chemical compound or composition according to any one of claims 7 to 9, wherein the side chain of one or more α-L-amino-acid residues in the β-strand forming section of peptide is selected from the group consisting of:

a hydrophobic group, or a group that has a considerable hydrophobic portion;

a branched or unbranched alkyl or aliphatic group;

a group that is branched at its connecting β-carbon atom;

an aromatic group;

an acidic or basic group; and

an amide- or hydroxyl-containing group.

11. A chemical compound or composition according to any preceding claim, wherein the side chain of one or more α-

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L-amino-acid residues in the β-strand-forming section of peptide hinders the stacking of β-sheets.

12. A chemical compound or composition according to claim 11, wherein the side chain of one or more α-L-amino-acid residues in the β-strand-forming section of peptide extends beyond the neighbouring side chains in the β-strand.

13. A chemical compound or composition according to any preceding claim, wherein the side chain of one or more α-L-amino-acid residues in the β-strand-forming section of peptide allows the compound or composition to be traced or detected.

14. A chemical compound or composition according to claim 13, wherein the side chain of one or more α-L-amino-acid residues in the β-strand-forming section of peptide is selected from the group consisting of:

an atom or group that contains a radioactive or magnetically active nucleus;

that of phenylalanine or tyrosine with one or more radioactive or magnetically active iodine or other halogen atoms substituted onto the aromatic ring;

a fluorescent, coloured, or other spectroscopically detectable group;

a group which contains an unpaired electron and thereby acts as a spin label;

a group which contains the 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL) group; and

a group which contains the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) group.

15. A chemical compound or composition according to any preceding claim, wherein the side chain of one or more α-L-amino-acid residues in the β-strand-forming section of

peptide is selected from the group consisting of the side chain of:

any naturally occurring α-L-amino-acid or synthetic derivative thereof; glycine; alanine; serine; cysteine; threonine; valine; leucine; isoleucine; methionine; phenylalanine; tyrosine; tryptophan; glutamine; asparagine; glutamate; aspartate; histidine; lysine; arginine; and
tert-leucine or β-hydroxyvaline.

16. A chemical compound or composition according to any preceding claim wherein the target β-strand is formed by the Alzheimer's Aβ peptide, and the β-strand-forming section of peptide binds specifically as a β-strand to part or all of the KLVFFAE sequence within the target β-strand in the parallel orientation, thereby forming a parallel β-sheet complex wherein consecutive residues of the β-strand-forming section of peptide lie directly opposite consecutive residues of the KLVFFAE sequence in the same order.

17. A chemical compound or composition according to any one of claims 1 to 15 wherein the target β-strand is formed by the Alzheimer's Aβ peptide, and the β-strand-forming section of peptide binds specifically as a β-strand to part or all of the KLVFFAE sequence within the target β-strand in the antiparallel orientation, thereby forming an antiparallel β-sheet complex wherein consecutive residues of the β-strand-forming section of peptide lie directly opposite consecutive residues of the KLVFFAE sequence in reverse order.

18. A chemical compound or composition as claimed in claim 17 wherein the β-strand-forming section of peptide comprises at least a four-residue segment of the amino-

acid sequence aa1-aa2-aa3-aa4-aa5-aa6-aa7, or a mimic thereof, where:

aa1 is α-L-lysine or α-L-arginine;

aa2 is α-L-leucine or α-L-lysine, or an Nα-substituted form thereof;

aa3 is α-L-valine or α-L-isoleucine;

aa4 is α-L-phenylalanine or α-L-tyrosine, or an Nα-substituted form thereof;

aa5 is α-L-phenylalanine or α-L-tyrosine;

aa6 is α-L-alanine, α-L-threonine, α-L-valine, α-L-isoleucine, α-L-leucine, α-L-methionine, α-L-lysine, or α-L-histidine, or an Nα-substituted form thereof;

aa7 is α-L-tryptophan or α-L-glutamate.

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19. A chemical compound or composition according to any preceding claim wherein the β-strand-forming section of peptide is preceded by, followed by, or otherwise attached to a distinct membrane-penetrating section of peptide which enables the β-strand-forming section of peptide to cross biological barriers such as cell membranes and the blood-brain barrier.

20. A chemical compound or composition according to claim 19 wherein the side chain of each residue in the membrane-penetrating section of peptide is selected from the group consisting of:

a basic or hydrophobic group; and a side chain of alanine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine, tryptophan, proline, histidine, lysine, or arginine.

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21. A chemical compound or composition as claimed in claim 19 or claim 20 wherein the membrane-penetrating section of peptide is made resistant to enzyme-catalysed proteolysis by the inclusion of α-D-amino-acid residues and/or Nα-substituted amino-acid residues.

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22. A chemical compound or composition according to any preceding claim wherein the β-strand-forming section of peptide has a free or acylated N terminus and a free, amidated, or esterified C terminus, or forms part of a larger peptide which has a free or acylated N terminus and a free, amidated, or esterified C terminus.

23. A chemical compound or composition according to any preceding claim wherein the β-strand-forming section of peptide is attached to another functional component.

24. A chemical compound or composition according to claim 23, wherein the functional component is selected from the group consisting of:

a component which strengthens the binding of the β-strand-forming section of peptide to the target β-strand;

a component which enhances specificity of association of the β-strand-forming section of peptide with the target β-strand;

a component which enables the β-strand-forming section of peptide to cross biological barriers such as cell membranes and the blood-brain barrier;

a component which causes the compound/composition to target specific organs, cells, or molecules;

a component which allows the compound/composition to be traced or detected;

an atom or group that contains a radioactive or magnetically active nucleus;

a fluorescent, coloured, or other spectroscopically detectable group;

a group which contains an unpaired electron and thereby acts as a spin label;

a group which contains the 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PROXYL) group or the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) group;

a solid matrix, resin, or support;

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an enzyme, hormone, antibody, transcription factor, or other protein molecule;

a group that binds specifically to a particular protein; and

a cytotoxic molecule.

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25. A chemical compound or composition according to claim 23 or claim 24, wherein attachment of the β-strand-forming section of peptide to the functional component is by means of an amide or ester linkage formed with the C-terminal carboxyl group or N-terminal amino group of the full peptide, or with a carboxyl, amino, or hydroxyl group of a side chain within the full peptide, or by means of a disulphide bridge formed with a thiol group of a side chain within the full peptide.

26. A chemical compound or composition according to any preceding claim wherein the β-strand-forming section of peptide associates with a target β-strand comprising the amino-acid sequence KLVFF (SEQ. ID. NO. 1).

27. A chemical compound or composition according to any preceding claim comprising one or more components which mimic the structure and action of said β-strand-forming section of peptide, wherein the components are formed by replacing one or more of the backbone peptide groups or side-chain groups of the β-strand-forming section of peptide by another chemical group of similar stereochemistry and ability to form favourable non-covalent interactions with the target β-strand.

28. A chemical compound or composition according to claim 25 wherein one or more of the backbone peptide groups (CONH) of the β-strand-forming section of peptide is/are replaced by one of the following groups: CSNH (thioamide); COO (ester); CSO, COS, CSS (thioester); $COCH_2$ (ketone); $CSCH_2$ (thioketone); SO_2NH (sulphonamide); $SOCH_2$

(sulphoxide); SO_2CH_2 (sulphone); SO_2O (sulphonate); and/or wherein one or more N-substituted backbone peptide groups of the β-strand-forming section of peptide is/are replaced by an N- or C-substituted form of one of the following groups: CSNH (thioamide); $COCH_2$ (ketone); $CSCH_2$ (thioketone); SO_2NH (sulphonamide); $SOCH_2$ (sulphoxide); SO_2CH_2 (sulphone); and/or wherein one or more of the side chains of the β-strand-forming section of peptide is/are replaced by another group having similar stereochemistry or arrangement of polar and non-polar atoms, maintaining those particular features which are essential for association with the target β-strand.

29. A method for inhibiting or reversing the association of a target β-strand into a β-sheet or β-fibre, comprising exposing the target β-strand to a chemical compound or composition according to any preceding claim and allowing or inducing the chemical compound or composition to associate with the target β-strand.

30. The use of a chemical compound or composition according to any one of claims 1 to 28 in the manufacture of a medicament for inhibiting or reversing the association of a target β-strand into a β-sheet or β-fibre.

31. A method for inhibiting or reversing the aggregation of proteins or peptides, comprising contacting the proteins or peptides with a chemical compound or composition according to any one of claims 1 to 28.

32. The use of a chemical compound or composition according to any one of claims 1 to 28 in the manufacture of a medicament for inhibiting or reversing the aggregation of proteins or peptides.

33. A method for assisting in the refolding of denatured or aggregated proteins or peptides, comprising contacting the aggregated proteins or peptides with a chemical compound or composition according to any one of claims 1 to 28.

34. The use of a chemical compound or composition according to any one of claims 1 to 28 in the manufacture of a medicament for assisting in the refolding of denatured or aggregated proteins or peptides.

35. The use of a chemical compound or composition according to any one of claims 1 to 28 in the preparation of a composition for the diagnosis, study, or treatment of a disease caused by the aggregation of proteins or peptides.

36. A method for inhibiting the oligomerisation or association of protein subunits, comprising exposing the protein subunits to a chemical compound or composition according to any one of claims 1 to 28.

37. The use of a chemical compound or composition according to any one of claims 1 to 28 in the manufacture of a medicament for inhibiting the oligomerisation or association of protein subunits.

38. The method of claim 36 or the use of claim 37 applied to inhibit the oligomerisation of an enzyme whose catalytic activity depends on its oligomerisation by the association of β-strands.

39. A method for indicating the presence or location of β-strands, β-sheets, or β-fibres, comprising exposing a test sample to a chemical compound or composition

according to any one of claims 1 to 28 which comprises a detectable moiety.

40. The use of a chemical compound or composition according to any one of claims 1 to 28 which comprises a detectable moiety, in the manufacture of an agent for indicating the presence or location of β-strands, β-sheets, or β-fibres.

41. A method for affinity or protein-renaturation chromatography, comprising the steps of covalently attaching a chemical compound or composition according to any one of claims 1 to 28 to a solid matrix, resin, or support; passing a test sample over the column; and separating the desired treated product from the column.

42. A combinatorial library comprising chemical compounds or compositions according to any one of claims 1 to 28.

43. A pharmaceutical compound or composition according to any one of claims 1 to 28.

44. A method of diagnosing, studying or treating a disease caused by the aggregation of proteins or peptides, comprising contacting the proteins or peptides with a chemical compound or composition according to any one of claims 1 to 28.

45. The method of claim 44, wherein the disease is selected from the following: Alzheimer's disease (AD); Parkinson's disease (PD); dementia; Dementia with Lewy Bodies (DLB); prion-related encephalopathies; bovine spongiform encephalopathy (BSE); Creutzfeldt-Jakob disease (CJD); kuru; dominantly inherited neurodegenerative diseases; Huntington's disease (HD), X-linked spinal and bulbar muscular atrophy (SBMA),

dentatorubral-pallidoluysian atrophy (DRPLA); spinocerebellar ataxia; type II diabetes mellitus; familial amyloid polyneuropathy; senile systemic amyloidosis; and dialysis-related amyloidosis.